GB2004/001256

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/205 A23L1/305

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

 $\begin{array}{ccc} \text{Minimum documentation searched (classification system followed by classification symbols)} \\ IPC & 7 & A61K & A23L \end{array}$ 

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, FSTA, WPI Data, PAJ

C. DOCUMENT	S CONSIDERED	TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 680 945 A (OMEARA PTY LTD) 8 November 1995 (1995-11-08) claims 1,2,4,8,10; examples 1-7 page 2, line 39 - page 3, line 47 page 4, lines 36-51	1-66

X Further documents are listed in the continuation of box C.	χ Patent family members are listed in annex.
<ul> <li>Special categories of cited documents:</li> <li>"A" document defining the general state of the art which is not considered to be of particular relevance</li> <li>"E" earlier document but published on or after the international filling date</li> <li>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</li> <li>"O" document referring to an oral disclosure, use, exhibition or other means</li> <li>"P" document published prior to the international filing date but later than the priority date claimed</li> </ul>	<ul> <li>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</li> <li>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</li> <li>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</li> <li>*&amp;* document member of the same patent family</li> </ul>
Date of the actual completion of the international search  30 June 2004	Date of mailing of the international search report $12/07/2004$
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2  NL – 2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  Fax: (+31-70) 340-3016	Authorized officer  Tallgren, A

GB2004/001256

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT					
ategory Citation of document, with indication, where appropriate, of the relevant passages    Relevant to claim No.					
(	GROSS C J ET AL: "Effect of development and nutritional state on the uptake, metabolism and release of free and acetyl-L-carnitine by the rodent small intestine."  BIOCHIMICA ET BIOPHYSICA ACTA. 3 NOV 1993, vol. 1170, no. 3, 3 November 1993 (1993-11-03), pages 265-274, XP008032228 ISSN: 0006-3002 page 265, paragraph 1 - page 266, paragraphs 1,6,7 tables 1-3 page 268, paragraph 1 - page 270, paragraph 3 page 272, paragraph 3 - page 273,	1-22, 42-62			
X	paragraphs 2,4,5  BOHLES H ET AL: "Improved N-retention during L-carnitine-supplemented total parenteral nutrition."  JPEN. JOURNAL OF PARENTERAL AND ENTERAL NUTRITION. 1984 JAN-FEB, vol. 8, no. 1, January 1984 (1984-01), pages 9-13, XP008032205  ISSN: 0148-6071  page 9, paragraphs 1,2,5  page 11, paragraphs 3,6,8 - page 12, paragraph 2	1-22, 42-66			
X	GREENWOOD R H ET AL: "Effects of L-carnitine on nitrogen retention and blood metabolites of growing steers and performance of finishing steers."  JOURNAL OF ANIMAL SCIENCE. JAN 2001, vol. 79, no. 1, January 2001 (2001-01), pages 254-260, XP002286196  ISSN: 0021-8812 page 254, paragraphs 1,4 page 256, paragraph 5 page 257, paragraph 5 page 257, paragraphs 2,4,6 page 259, paragraph 5 - page 260, paragraphs 1,3 tables 1,2	1-22, 42-66			

GB2004/001256

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT					
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
X	LACOUNT D W ET AL: "Responses of dairy cows during early lactation to ruminal or abomasal administration of L-carnitine." August 1995 (1995-08), JOURNAL OF DAIRY SCIENCE. AUG 1995, VOL. 78, NR. 8, PAGE(S) 1824 - 1836, XPO02286406 ISSN: 0022-0302 page 1824, paragraph 1 page 1825, paragraph 3 table 1 page 1827, paragraph 3-5 page 1828, paragraph 3 - page 1829, paragraph 2 page 1835, paragraph 2	1-22, 42-66			
X	LACOUNT D W ET AL: "Dose response of dairy cows to abomasal administration of four amounts of L-carnitine."  April 1996 (1996-04), JOURNAL OF DAIRY SCIENCE. APR 1996, VOL. 79, NR. 4, PAGE(S) 591 - 602, XP002286407 ISSN: 0022-0302 page 591, paragraph 3 page 593, paragraph 3 page 594, paragraph 3 page 594, paragraph 3 page 596, paragraph 3 page 597, paragraph 3 page 597, paragraph 3 page 597, paragraph 3 tables 1,2,4,7	1-22, 42-66			
X	LACOUNT D W ET AL: "Ruminal degradation and dose response of dairy cows to dietary L-carnitine."  February 1996 (1996-02), JOURNAL OF DAIRY SCIENCE. FEB 1996, VOL. 79, NR. 2, PAGE(S) 260 - 269, XP002286408  ISSN: 0022-0302  page 260, paragraphs 1,2,4 - page 261, paragraph 2  table 1  page 262, paragraph 2  page 263, paragraphs 4,5  page 267, paragraph 3	1-22, 42-66			
X	WO 01/95915 A (SIGMA TAU HEALTHSCIENCE SPA; POLA PIETRO (IT)) 20 December 2001 (2001-12-20) claims 1,3,9-14 page 1, paragraph 1 - page 2, paragraph 1 page 6, paragraph 3 - page 9, paragraph 1	1-41			

PCT/GB2004/001256

### INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: 42-66 (partially) because they relate to subject matter hot required to be searched by this Authority, namely:
Rule 39.1(v) PCT - Presentation of information Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. X Claims Nos.: 1-9, 23-28,42-44,47-49 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  see FURTHER INFORMATION sheet PCT/ISA/210
See Tokynek Thi Skinki ton Sheet Toy, 1979 215
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 42-66 (partially)

Rule 39.1(v) PCT - Presentation of information Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box II.2

Claims Nos.: 1-9, 23-28,42-44,47-49

Claims 1-9,23-28,42-44, 47-49 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the agents comprising carbohydrates, amino acids and proteins as disclosed in page 4 lines 1-2, page 5 lines 15-18, page 7 lines 19-22, claim 10.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

GB2004/001256

	Patent document cited in search report		Publication date		Patent family member(s)	Publication date
	EP 0680945	A	08-11-1995	AU EP ZA JP	1780395 A 0680945 A2 9504224 A 8333313 A	09-11-1995 08-11-1995 22-01-1996 17-12-1996
	WO 0195915	Α	20-12-2001	IT AU CA CN CZ DE EP HU WO PL SK US	RM20000323 A1	14-12-2001 15-05-2004 24-12-2001 20-12-2001 13-08-2003 17-07-2002 03-06-2004 19-03-2003 28-11-2002 20-12-2001 11-04-2002 25-08-2003 09-05-2002 01-04-2003 12-06-2003
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### PATENT COOPERATION TREATY

REC'D 0 8 JUL 2004 From the INTERNATIONAL SEARCHING AUTHORITY To: WRITTEN OPINION OF THE see form PCT/ISA/220 INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1) Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet) Applicant's or agent's file reference FOR FURTHER ACTION See paragraph 2 below see form PCT/ISA/220 Priority date (day/month/year) International filing date (day/month/year) International application No. 20.03.2003 22.03.2004 PCT/GB2004/001256 International Patent Classification (IPC) or both national classification and IPC A61K31/205, A23L1/305 Applicant THE UNIVERSITY OF NOTTINGHAM This opinion contains indications relating to the following items: 1. Basis of the opinion Box No. I Box No. II Non-establishment of opinion with regard to novelty, inventive step and industrial applicability Box No. III Lack of unity of invention ☐ Box No. IV Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial Box No. V applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited Certain defects in the international application ☐ Box No. VII ☐ Box No. VIII Certain observations on the international application **FURTHER ACTION** If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered. If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. For further options, see Form PCT/ISA/220. For further details, see notes to Form PCT/ISA/220. Authorized Officer Name and mailing address of the ISA: European Patent Office - P.B. 5818 Patentlaan 2

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International application No. PCT/GB2004/001256

	Box	No. I Basis of the opinion				
1.	With regard to the <b>language</b> , this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.					
	I	This opinion has been established on the basis of a translation from the original language into the following anguage , which is the language of a translation furnished for the purposes of international search under Rules 12.3 and 23.1(b)).				
2.		regard to any <b>nucleotide and/or amino acid sequence</b> disclosed in the international application and ssary to the claimed invention, this opinion has been established on the basis of:				
	a. typ	pe of material:				
		a sequence listing				
		table(s) related to the sequence listing				
	b. format of material:					
		in written format				
		in computer readable form				
	c. tim	e of filing/furnishing:				
		contained in the international application as filed.				
		filed together with the international application in computer readable form.				
		furnished subsequently to this Authority for the purposes of search.				
3.	i (	n addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.				
4.	Addit	ional comments:				

International application No. PCT/GB2004/001256

	Box	No. II	Priority
1.		The fol	lowing document has not been furnished:
		$\boxtimes$	copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
			translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).
			quently it has not been possible to consider the validity of the priority claim. This opinion has neless been established on the assumption that the relevant date is the claimed priority date.
2.		has be	pinion has been established as if no priority had been claimed due to the fact that the priority claim en found invalid (Rules 43 <i>bis</i> .1 and 64.1). Thus for the purposes of this opinion, the international ate indicated above is considered to be the relevant date.
3	Add	litional c	heervations if necessary

International application No. PCT/GB2004/001256

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability					
The	The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:				
	the entire international application	on,			
$\boxtimes$	claims Nos. 1-9,23-28,42-62 (p	artially), 63-66			
bec	ause:				
⊠	the said international application, or the said claims Nos. 42-62 relate to the following subject matter which does not require an international preliminary examination (specify):				
	see separate sheet				
$\boxtimes$	the description, claims or drawi 1-9,23-28,42-44,47-49,63-66	ngs <i>(indicate particular elements below)</i> or said claims Nos. are so unclear that no meaningful opinion could be formed <i>(specify)</i> :			
	see separate sheet				
	the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.				
	no international search report h	as been established for the whole application or for said claims Nos.			
	the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:				
	the written form	□ has not been furnished			
		does not comply with the standard			
	the computer readable form	☐ has not been furnished			
		☐ does not comply with the standard			
	the tables related to the nucleon not comply with the technical r	tide and/or amino acid sequence listing, if in computer readable form only, do equirements provided for in Annex C-bis of the Administrative Instructions.			
	See separate sheet for further	details			

International application No. PCT/GB2004/001256

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

2-20,22,24-41,45-62

No:

No:

Claims

1,21,23,42-44,63-66

Inventive step (IS)

Yes: Claims

Claims

1-66

Industrial applicability (IA)

Yes: Claims

1-41, 63-66

No: Claims

42-62

2. Citations and explanations

see separate sheet

PCT/GB2004/001256

### ITEM III

Claims 1-9,23-28,42-44, 47-49 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the agents comprising carbohydrates, amino acids and proteins as disclosed in page 4 lines 1-2, page 5 lines 15-18, page 7 lines 19-22, claim 10.

Claims 42-62 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 42-62 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. However such claims as present claims 42-62 do not appear to be novel and inventive for reasons explained later in this written opinion.

Claims 63-66 contain references to the description and examples. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

It is clear from the description on pages 3 and page 4 lines 1-2, page 5 lines 15-18, page 7 lines 19-22, claim 10 that the following features are essential to the definition of the invention:

- (1) Carnitine
- (2) Agent (carbohydrate, amino acid and protein)

Since independent claims 63-66 do not contain these features they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

### ITEM V

- 1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:
  - D1: EP-A-0 680 945 (OMEARA PTY LTD) 8 November 1995 (1995-11-08)
  - D2: GROSS C J ET AL: "Effect of development and nutritional state on the uptake, metabolism and release of free and acetyl-L-carnitine by the rodent small intestine." BIOCHIMICA ET BIOPHYSICA ACTA. 3 NOV 1993, vol. 1170, no. 3, 3 November 1993 (1993-11-03), pages 265-274, XP008032228 ISSN: 0006-3002
  - D3: BOHLES H ET AL: "Improved N-retention during L-carnitine-supplemented total parenteral nutrition." JPEN. JOURNAL OF PARENTERAL AND ENTERAL NUTRITION. 1984 JAN-FEB, vol. 8, no. 1, January 1984 (1984-01), pages 9-13, XP008032205 ISSN: 0148-6071
  - D4: GREENWOOD R H ET AL: "Effects of L-carnitine on nitrogen retention and blood metabolites of growing steers and performance of finishing steers." JOURNAL OF ANIMAL SCIENCE. JAN 2001, vol. 79, no. 1, January 2001 (2001-01), pages 254-260, XP002286196 ISSN: 0021-8812
  - D5: LACOUNT D W ET AL: "Responses of dairy cows during early lactation to ruminal or abomasal administration of L-carnitine." August 1995 (1995-08), JOURNAL OF DAIRY SCIENCE. AUG 1995, VOL. 78, NR. 8, PAGE(S) 1824 1836, XP002286406 ISSN: 0022-0302
  - D6: LACOUNT D W ET AL: "Dose response of dairy cows to abomasal administration of four amounts of L-carnitine." April 1996 (1996-04), JOURNAL OF DAIRY SCIENCE. APR 1996, VOL. 79, NR. 4, PAGE(S) 591 602, XP002286407 ISSN: 0022-0302
  - D7: LACOUNT D W ET AL: "Ruminal degradation and dose response of dairy cows to dietary L-carnitine." February 1996 (1996-02), JOURNAL OF DAIRY SCIENCE. FEB 1996, VOL. 79, NR. 2, PAGE(S) 260 269, XP002286408 ISSN: 0022-0302
  - D8: WO 01/95915 A (SIGMA TAU HEALTHSCIENCE SPA; POLA PIETRO (IT)) 20 December 2001 (2001-12-20)

#### 2. NOVELTY OBJECTIONS

D1 describes the use of carnitine in feed and food supplements with amino acids to improve carnitine retention. (page 2, line 39- page 3, line 47, page 4 lines 36-51). Consequently, the subject matter of claims 1,21,23,42-44, 63-66 is considered as being not new in view of D1 (Art 33 (2) PCT).

D2 describes the use of carnitine in feed supplements (protein, amino acids and carbohydrates (sucrose) to improve carnitine retention. Samples studied from intestine and mucosa. (page 265, paragraph 1- page 266, paragraphs 1,6,7, page 268, paragraph 1- page 270, paragraph 3, page 272, paragraph 3- page 273, paragraphs 2,4,5). Consequently, the subject matter of claims 1,42-44,63-66 is considered as being not new in view of D2 (Art 33 (2) PCT).

D3 describes the use of carnitine in feed supplements (protein, amino acids and carbohydrates (sucrose) to improve carnitine retention. Samples studied from serum and urine. (page 9, paragraph 1,2,5, page 11, paragraphs 3,6,8- page 12, paragraph 2). Consequently, the subject matter of claims 1,42-44,63-66 is considered as being not new in view of D3 (Art 33 (2) PCT).

D4 describes the use of carnitine in feed supplements (protein, amino acids and carbohydrates (molasses) to study carnitine retention. Samples studied from kidney, pelvic, heart, blood, plasma (page 254 paragraph 1,4, page 256, paragraph 5, page 257, paragraph 2,4,6, page 259, paragraph 5 page 260 paragraph 1,3, tables 1,2). Consequently, the subject matter of claims 1,42-44,63-66 is considered as being not new in view of D4 (Art 33 (2) PCT).

D5 describes the use of carnitine in feed supplements (protein, amino acids, molasses and carbohydrates) to study carnitine retention. Samples studied from, blood, tissue, muscle, liver (page 1824 paragraph 1, page 1825, paragraph 3, page 1827, paragraph 3-5, page 1828, paragraph 3- page 1829 paragraph 2, page 1835 paragraph 2, table 1). Consequently, the subject matter of claims 1,42-44,63-66 is considered as being not new in view of D5 (Art 33 (2) PCT).

D6 describes the use of carnitine in feed supplements (protein, amino acids and carbohydrates) to study carnitine retention. Samples studied from plasma, blood,urine. (page 591, paragraph 3, page 593, paragraph 3, page 594, paragraph 3, page 596,

# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/GB2004/001256

paragraph 3, page 597, paragraphs 3,4, page 601, paragraph 2, tables 1,2,4,7). Consequently, the subject matter of claims 1,42-44,63-66 is considered as being not new in view of D6 (Art 33 (2) PCT).

D7 describes the use of carnitine in feed supplements (protein, amino acids, molasses and carbohydrates) to study carnitine retention. Samples studied from plasma, blood,urine. (page 260, paragraphs 1,2,4- page 261, paragraph 2, page 262, paragraph 2, page 263, paragraph 45, page 267, paragraphs 3). Consequently, the subject matter of claims 1,42-44,63-66 is considered as being not new in view of D7 (Art 33 (2) PCT).

D8 describes the use of carnitine in food supplements (protein, amino acids, carbohydrates) to improve muscle performance (page 1, paragraph 1- page 2, paragraph 1, page 6, paragraph 3- page 9, paragraph 1). Consequently, the subject matter of claims 1,21,23, 63-66 is considered as being not new in view of D8 (Art 33 (2) PCT).

#### 3. INVENTIVE STEP OBJECTIONS

Dependent claims 2-20,22,24-41,45-62 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty or inventive step, the reasons being as follows:

The features of dependent claims 2-20,22,24-41,45-62 have already been employed for the same purpose (see documents D1 (claims 2-10,15-20,22 24-29, 34-41, 45-51,55-62), D2-D7 (claims 2-20, 45-62, D8 (claims 2-20, 22,24-41). It would therefore be obvious to the person skilled in the art, to apply these features with corresponding effect. Consequently, the subject matter of claims 2-20,22,24-41,45-62 is considered as being not inventive in view of D1-D8 (Art 33(3) PCT).

None of the claimed compositions, uses or methods are considered to be inventive in view of D1-D8 (Art 33(3) PCT). Having regard to the claimed compositions, uses or methods and the prior art known (D1-D8), it is considered that the man skilled in the art would regard these compositions, uses or methods of the present invention (as far as novel) as an obvious alternative to those known. Therefore, unless an unexpected effect for the present compositions, uses or methods (as far as novel) over the prior art disclosure from D1-D8 can be demonstrated, these compositions, uses or methods do not fulfill the requirements of Art 33(3) PCT.